REMARKS

Claims 17 and 40-42 are pending. Claims 17 and 40-42 have been amended to more clearly describe the claimed invention. Support for claims 17 and 40-42 as amended is found throughout the specification as filed and at original claims 17 and 39 and 40-42. No new matter has been added.

Claim Objections

Claim 17 was objected to because, as previously worded, "motif" should have been "motifs." Office Action mailed February 21, 2008 (Office Action). Claim 17 has been amended to correct informalities. Applicants respectfully request reconsideration and withdrawal of the objection.

Rejections under 35 U.S.C. § 103

Claims 17 and 40-42 were rejected under 35 U.S.C. § 103 as allegedly rendered obvious by Smetsers, et al., (Smetsers) in view of Torrence et al., (Torrence), and Bennett et al., (Bennett). Office Action at page 2. Applicants respectfully traverse.

To establish prima facie obviousness, the Patent Office must demonstrate that a cited prior art reference or combination of references teaches or suggests each limitation of the claims. In re Royka, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974); In re Wilson, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970). The Supreme Court further held that a finding of obviousness requires identification of "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *KSR Int'l Co. v. Teleflex*, 127 S.Ct. 1727 (2007). Because the cited references do not disclose every element of the present claims, the Examiner has not established a prima facie case for obviousness.

Claim 17 recites methods of identifying at least one antisense sequence for inhibiting expression of a preselected target nucleic acid. The claim includes the step of eliminating from a set of candidate antisense sequences, any candidate antisense sequences comprising negative predictor sequence motif 5'-GGA-3'. The Examiner contends that this step is rendered obvious by Smetsers. See Office Action at page 3. Smetsers surveyed antisense literature and databases and identified certain oligonucleotide motifs that were statistically over-represented and certain motifs that were

under-represented among 206 previously reported antisense compounds. Smetsers concluded that "there is a bias in the sequence composition" of reported antisense compounds and speculated that these biased sequence motifs "probably play a role in the effectiveness of the oligonucleotides." Smetsers at page 66. That is, Smetsers suggests that over-represented motifs may instill some positive property in the antisense compound and under-represented motifs may instill some negative property.

Without acquiescing to the soundness of the study or the accuracy of the conclusions in Smetsers, Applicants simply note that 5'-GGA-3' is not among the under-represented motifs. Thus, there is nothing in Smetsers that would render obvious the step of eliminating from the set of candidate antisense sequences, any candidate antisense sequences comprising negative predictor sequence motif 5'-GGA-3'. The Examiner relies on the inclusion of 5'-TCC-3' in the under-represented oligonucleotides noting that 5'-TCC-3' is the complement of 5'-GGA-3'. See Office Action at page 3. The Examiner reasons that "one of ordinary skill in the art would expect that if a motif binding to its complementary sequence has a physical characteristic that negatively affects antisense activity, the same effect should occur when the complementary sequence is present in the antisense strand." Id. Thus, the Examiner asserts that sequence motifs are likely to have the same effect whether they are in an antisense oligonucleotide or its target. That assertion is contrary to the teaching of Smetsers.

Smetsers speculates that the observed bias for or against certain motifs may be due to "nonantisense as well as antisense mechanisms, for example, by increasing uptake or changing cellular localization." Smetsers at 66. Smetsers also notes that "these nucleotide motifs induce a biologic effect that is caused by protein binding." Id. at 63. There is no reason to expect that a complementary motif is likely to impart the same properties in such respects. More to the point, if the Examiner's reasoning were correct, then the under-represented and over-represented lists in Smetsers ought to include certain motifs *and their complements*, but that is not the case. For example, Smetsers reports that 5'-AA-3' is under-represented, but does not report that its complement, 5'-TT-3', is likewise under-represented.

Further, as relied on by the Examiner, Smetsers reports that 5'-TCC-3' is under-represented among antisense compounds, however, its complement 5'-GGA-3' is not under-represented. In fact, Smetsers reports that both 5'-GGAC-3' and 5'-GG-3' are *over*-represented among reported antisense compounds. See Smetsers, Table 1 at page 65. Thus, Smetsers actually teaches away

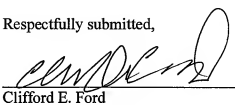
from the present invention of eliminating candidate antisense sequences comprising negative predictor sequence motif 5'-GGA-3' by suggesting that 5'-GGAC-3' and 5'-GG-3' are favorable motifs.

Neither of the other cited references remedies the deficiency of Smetsers in rendering obvious the step of eliminating from a set of candidate antisense sequences, any candidate antisense sequences comprising negative predictor sequence motif 5'-GGA-3'. Though Bennett discloses certain oligonucleotides that include the sequence motif 5'-CCAC-3' and that lack either motif 5'-GGA-3' or 5'-GGGG-3', Bennett does not suggest the claimed methods having the recited steps. Finally, Torrence also fails to discuss or suggest the step avoiding the 5'-GGA-3' motif. In fact two of the six most preferred antisense sequences in Torrence include 5'-GGA-3'. See SEQ ID NOs.: 15 and 19.

Thus, the references, whether considered separately or together, fail to teach every element of claim 17. Claims 40-42 each ultimately depend from claim 17 and are likewise nonobvious. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 17 and 40-42 under 35 U.S.C. § 103.

Applicant believes that the foregoing constitutes a full and complete response to the Office Action. Withdrawal of the pending rejections and reconsideration of the claims is respectfully requested. If the Examiner believes that there are any remaining issues in the case that could be resolved by a telephonic interview, the Examiner is encouraged to contact the Agent for Applicant listed below to discuss any outstanding matters.

Respectfully submitted,



Clifford E. Ford
Reg. No. 52,903

Date: 5/21/2008
Isis Pharmaceuticals, Inc.
1896 Rutherford Road
Carlsbad, CA 920078
Direct Dial: 760 603-2784